REMARKS

The Office Action and the cited and applied references have been carefully studied. No claims are allowed. Claims 9-11, 13, 21 and 40-52 presently appear in this application (with claims 21 and 50-52 withdrawn from consideration by the examiner) and define patentable subject matter warranting their allowance. While applicants do not concede that claims 21 and 50-52 do not encompass the elected specie, it is understood that upon allowance of a generic claim, applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of allowed generic claim. Reconsideration and allowance are hereby respectfully solicited.

Briefly, the present invention provides antipathogenic synthetic peptides which are not derived from natural antibacterial peptides. Antibiotic resistance is presently a particularly severe problem and there is an absolute need to develop new sources of antimicrobial substances. Short antibacterial peptides (10-30 residues) have been identified in nature as part of the intrinsic defense mechanisms of many organisms. A problem with using some of the natural antibacterial peptides is that these

peptides have potential side effects because, in addition to being lytic to bacteria cells, they also lyse normal red blood cells. It has been reported in the art that derivatization of antibacterial natural peptides produced peptides which remain lytic to bacteria while being less lytic or not lytic at all to red blood cells. This is different from the present claimed synthetic peptides which are not derived from natural antibacterial peptides.

Claims 9-11, 13, 38, and 40-49 have been rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. The examiner states:

> The specification asserts that the claimed peptides are effective to cause lysis of pathogenic cells. However, there is no evidence that this is the case. Certainly, there is data in the specification (pages 48-53) which shows that selected peptides can inhibit growth of bacteria, fungi and adenocarcinoma cells (Also, tables 1 and 2, pages 28-30). However, merely because a compound can inhibit growth of pathogenic cells does not mean that this inhibition has occurred as a result of cytolysis.

This rejection is respectfully traversed.

With due respect to the examiner, the examiner is incorrect that there is no evidence in the specification that the claimed peptide is cytolytic to pathogenic cells. The examiner is also incorrect in stating that there are no "working examples" which show that the claimed peptides are

cytolytic and that there is no direction or guidance provided in the specification which would teach the skilled microbiologist how to determine which of the peptides that inhibit pathogenic cell growth will also induce cytolysis. The present specification teaches that the presently claimed peptides damage membranes in model vesicles which mimic bacterial membranes, and further demonstrates that a direct correlation exists between the potential of such peptides to damage model vesicles and their lytic activity against *E. coli* (see Fig. 14 and page 43, line 26 to page 44, line 8). Thus, the ability of the instant peptides to induce cytolysis is supported in the present specification, and therefore the presently claimed invention is certainly enabling to those of skill in the art.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 9 and 11 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner indicated that the term "the positive charged amino acid" lacks antecedent basis in claim 41 from which claim 9 depends. This rejection is obviated by the amendments to claims 9 and 11.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 9-11, 40, 41, 47 and 48 have been rejected under 35 U.S.C. §102(e) as being anticipated by Maloy, U.S. Patent No. 5,792,831. The examiner refers to applicants' statement in the previous response that the new claims do not permit all of the amino acids of the peptide to be of the D-configuration, or all of the chiral amino acids to be of the D-configuration as long as an alpha-helix breaker moiety is present, and states that this particular statement is actually not true. Furthermore, the examiner holds that, even if this statement were to be true, the stereochemical requirements of the claims are met if the following condition is met: at least one but not all of amino acids is a D-amino acid. This requirement, according to the examiner, is met by each of SEQ ID NOs: 1-8 of Maloy. This rejection is respectfully traversed.

The peptides disclosed by Maloy are analogues of magainin peptides of 21-23 amino acid residues where each amino residue is either a glycine residue or a D-amino acid residue, as disclosed at column 16, line 62 cited by the examiner (also see column 1, lines 22-26). Amendments to claims 40, 41, 47 and 48 defining enantiomeric peptides of up to 12 amino acids, with the proviso that none of the amino acid residues is glycine, clearly distinguish the present claims over Maloy and overcome the anticipation rejection.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 9-11, 40-42, 47 and 48 have been rejected under 35 U.S.C. 102(a) as being anticipated by Lee (WO 97/02286). The examiner states that Lee discloses antibiotic peptides which contain both D- and L-amino acids and which do not lyse blood cells. The examiner cites in particular the peptide KKYIKKVFVFK-NH2 (named by Lee as M22), in which one or more L-amino acids (but not all) have been replaced with D-amino acids (Table 11, pages 18-19). This rejection is obviated by the amendments to claims 40, 41, 47 and 48 to exclude tyrosine as an amino acid residue in the presently claimed peptide.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 9-11, 38, 40, 41, 47 and 48 have been rejected under 35 U.S.C. 103 as being unpatentable over Shai (*J. Biol. Chem.* 271:7305, 1996). The examiner states that Shai teaches at page 7306, Table 1, several peptides that are antibacterial but non-hemolytic, and which would otherwise meet the requirements of the claims were it not for the exclusion of SEQ ID NOs: 1, 12, 14 and 23. The examiner further states that, as indicated in the previous Office Action, this rejection is directed to close structural

homologues of SEQ ID NOs: 1, 12 and 14, such as, for example, by replacing a phenylalanine residue with a phenethylglycine residue. The examiner refers to applicants' statement in the previous response regarding the examiner's example of an amino acid not found in nature, H_2N-CH(CH_2-CH_2-COX)COX, wherein X is

ethylenediamine, which states:

> contrary to the examiner's assertion, this residue is not an amino acid at all and therefore cannot be an amino acid not occurring in nature. While this compound can be designated a chemical derivative of a natural amino acid, no peptide biochemist would regard this compound as being encompassed within the definition of an amino acid. In fact, this same inventor of the instant application and biochemist recognized as an expert in the area of peptide biochemistry and author or co-author of innumerable scientific publication, and the response was unanimous this is clearly not an amino acid.

The examiner holds that applicants have provided neither evidence nor reasoning as to why the skilled peptide chemist would come to believe that the compound in question is not an amino acid, and provides the following arguments to indicate that the compound in question is an amino acid: (i) the spatial relationship between the "C-terminal" carbonyl group and the alpha-amino group is identical to that which is found in glutamine, (ii) the number of carbon atoms which separates

the two groups is identical in the amino acid in question versus glutamine, (iii) the spatial relationship between "beta" carbonyl group and the alpha-amino group is identical to that which is found in glutamine, and (iv) the number of carbon atoms which separates the two groups is identical in the amino acid in question versus glutamine. Based on the above reasoning the examiner maintains that the compound in question is an amino acid. This rejection is respectfully traversed.

Applicants respectfully point out that the question of obviousness is determined relative to a hypothetical person of ordinary skill in the art and not to one of extraordinary skill such as a skilled peptide chemist. Attached hereto is the following definition of amino acids from "Principles of Biochemistry", Lehninger, Nelson and Cox, Worth Publishers, 2nd Edition, 1993, page 60 (copy enclosed): "Amino acids, an important family of molecules that serve primarily as monomeric subunits of proteins, contain at least two different kinds of functional groups: an amino group and a carboxyl group." Thus, applicants reemphasize that an ordinary person skilled in the art would not regard this compound as being encompassed within the definition of an amino acid.

Furthermore, the peptide disclosed by Shai contains 33 amino acids along with the residue glycine and is therefore very distant from the presently claimed peptides.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claim 38 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Maloy or Lee separately. While applicants do not concede to the examiner's position regarding obviousness of a composition in view of the distinctions between the present invention and Maloy or Lee as discussed above in the separate anticipation rejections over Maloy and Lee, these rejections are made moot by the cancellation of claim 38 without prejudice.

Claims 9-11, 38, 40, 41, 47 and 48 have been rejected under 35 U.S.C. §103 as being unpatentable over Paradies (U.S. 4,874,950). The examiner states that Paradies discloses the antibiotic gramicidin S, a cyclic peptide that contains two D-amino acids and has a net charge of +1. The examiner responds to applicants' previous argument that the fact that a compound inhibits pathogenic cell growth is not sufficient to conclude that the inhibition has occurred as a result of cytolysis by stating that one of ordinary skill in the art would expect that if a compound is cytotoxic to

microorganisms, then it is cytolytic. This rejection is respectfully traversed.

The examiner's position above appears to be at odds with his position regarding enablement in this same Office Action, where the examiner asserts that "merely because a compound can inhibit growth of pathogenic cells does not mean that this inhibition has occurred as a result of cytolysis". Applicants concur with the examiner's assertion that the demonstration of inhibition of pathogenic growth is not evidence that this inhibition has occurred as a result of cytolysis. In view of this concurrence, the examiner's contradictory position here on the issue of obviousness is untenable.

Furthermore, the statement by the examiner that all the experiments conducted on pathogenic cells disclosed in the specification were limited to showing inhibition of cell growth is not correct. As discussed above in response to the enablement rejection, the ability of the presently claimed peptides to induce cytolysis was clearly demonstrated either by the peptide-induced membrane permeation model and/or by transmission electron microscopy (see specification, page 44 and Fig. 14).

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 9-11, 38, 40, 41, 47 and 48 have been rejected under 35 U.S.C. §103 as being unpatentable over Jacob (U.S. 5,635,479). The examiner states that Jacob discloses peptides that can be used to inhibit growth of cancer cells, and to treat cancer patients. From among the disclosed peptides, the examiner cites SEQ ID NOs:115 and 117 in which all of the chiral amino acids are of the D-configuration, but which also contain glycine. The two peptides are said to extend the life of rats which had been injected with ovarian teratoma cells. The examiner admits that the reference does not explicitly state that the peptides are more effective at killing cancer cells than they are at inducing hemolysis. However, the examiner repeats here that the present claims encompass peptides which meet both of the following conditions: (a) at least one glycine is present, and (b) all amino acids other than glycine are of the D-configuration. This rejection is respectfully traversed.

The presently amended claims exclude peptides with glycine and peptides in which all the amino acids other than glycine are of the D-configuration. In addition, the presently claimed peptides contain 6-12 amino acids, whereas Jacob's peptides of SEQ ID NOs:115 and 117 have either glycine or are all of the D-configuration and have 22 amino acid residues. Moreover, Jacob's peptides of SEQ ID NOs:115 and

117 were never shown to be cytolytic or to lack hemolytic activity. As all of the claims require a ratio of hydrophobic to positively charged amino acids such that the peptide is cytolytic to pathogenic cells but does not cause cytolysis of red blood cells, the examiner has not met his burden for establishing a *prima facie* case of obviousness.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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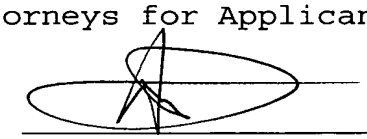
By 

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